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(54) Title: POLYALKYLENE OXIDE CONTAINING QUATERNARY AMMONIUM ANTIMICROBIAL AGENTS

(57) Abstract

Ophthalmic compositions of quaternary ammonium compounds containiing a polyalkylkene oxide moiety useful as antimicrobial agents are disclosed. Methods for using the compositions are also disclosed. In addition, polymers with no molecular weight distribution are disclosed.

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# Polyalkylene Oxide Containing Quaternary Ammonium Antimicrobial Agents

## Background of the Invention

This invention is directed to ophthalmic compositions comprising quaternary ammonium compounds containing a polyalkylene oxide moiety. Some of the compounds are new. These polymeric compounds are useful as antimicrobial agents. The invention is also directed to exact molecular weight quaternary ammonium compounds containing a polyalkylene oxide moiety.

The antimicrobial activity of quaternary ammonium compounds is known; see for example, Petrocci, et al., *Dev. Ind. Micro.*, 20, Chapter 1 (1978); Petrocci, *Disinfection, Sterilization and Preservation*, Third Edition, Chapter 14 (1983); Hugo, et al., *Principles and Practices of Disinfection, Preservation and Sterilization*, Chapter 2 (1982). In addition, U.S. Patent No. 4,567,302 and EP 214,850 disclose quaternary ammonium compounds which contain polyalkylene oxide units; however, neither disclose the compounds of the present invention. U. S. Patent No. 4,110,263 discloses biquaternary ammonium compounds useful in cleansing compositions in combination with a detergent. The compounds are useful for shampoos, skin cleansers, baby and bubble baths. WO 91/09522 discloses ophthalmic compositions useful in the care of contact lenses. The compositions contain a quaternary ammonium substituted matrix material selected from proteinaceous materials, carbohydrate materials, or mixtures thereof. Unlike the compounds used in the present invention, the quaternary ammonium groups are substituents on a matrix material backbone rather than being part of the polyalkelene oxide polymer backbone. EP 0153 435 A1 discloses hair care compositions containing diquaternary nitrogen polyethylene glycol derivatives. CA 110(3), 23322K discloses the preparation of certain pentane diammonium debiomides as antimicrobial agents.

Polymeric disinfectants, in general, have shown weak antifungal activity although they exhibit remarkable antimicrobial activity against other organisms. This invention

discloses the use of particular polymeric disinfecting agents which have a broad spectrum of antimicrobial activity, including antifungal activity.

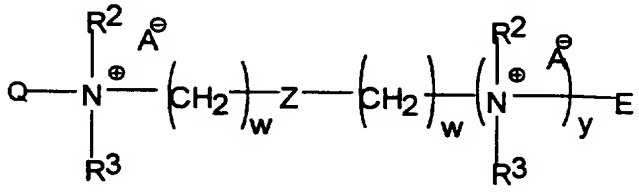
## Summary of the Invention

This invention is directed to contact lens care formulations and ophthalmic formulations comprising certain quaternary ammonium compounds containing a polyalkylene oxide moiety. The compounds are antimicrobials and are useful as disinfecting agents and preservatives.

The invention is also directed to methods for using the compounds to disinfect contact lenses and preserve contact lens care solutions and ophthalmic formulations.

## Detailed Description of Preferred Embodiments

The ophthalmic formulations of this invention contain quaternary ammonium compounds containing a polyalkylene oxide moiety of the following general formula:



wherein:

w = 0-10;

y = 0 or 1;

$R^2$ and $R^3$ are the same, or different, and are selected from the group: $C_1$-$C_{20}$ alkyl, benzyl and substituted benzyls, aromatics and substituted aromatics and cycloalkyl and substituted cycloalkyls; Q and E are the same, or different, and are selected from the group: H, $C_1$-$C_{20}$ alkyl, $C_2$-$C_6$ alkene, benzyl and substituted benzyls, aromatics and substituted aromatics, cycloalkyl and substituted cycloalkyls; heteroatom containing long alkyl chain, silane and siloxane; but, either Q and/or E must contain an alkyl structure of at least a $C_5$ alkyl, but not more than a $C_{20}$ alkyl moiety; Z has the following structure:

$$[(CH_2\text{-}CH(R)\text{-}O)_n\text{-}(CH_2\text{-}CH(R')\text{-}O)_m]_x$$

wherein:

R and R' are different and can be H, methyl or ethyl;

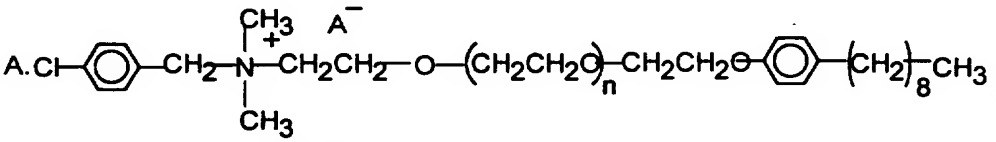
n = 1-4

m = 0-4

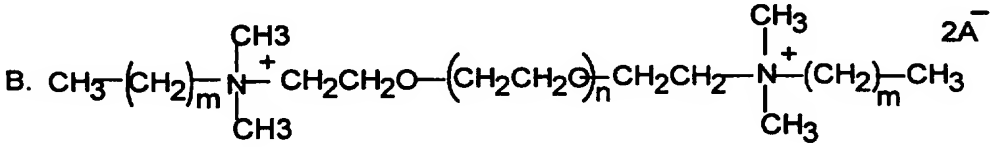
x = 1-50; and

$A^-$ is a pharmaceutically acceptable anion, e.g. $Cl^-$, $Br^-$, $I^-$, $CH_3(C{=}O)\text{-}O^-$, etc.

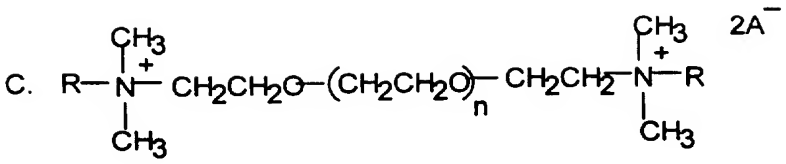
Preferred compounds within the above defined structure have the following formulas:

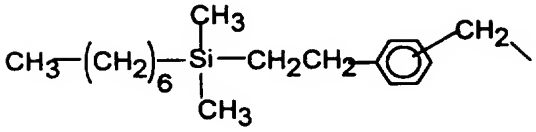


wherein n = 4-13



wherein m = 7-17, n = 0-14

C. 

| | R | n |
|---|---|---|
| 1. |  | 6-8 |
| 2. |  | 6-8 |
| 3. |  | 6-8 |

The compounds are formulated into disinfecting and storage solutions for all types of contact lenses. The formulations can also be used as preserved saline solutions for rinsing and as an in the eye drop to rehydrate a lens and/or to soothe the eye. The compounds are also useful as preservatives in ophthalmic formulations other than lens care solutions, such as, ophthalmic pharmaceutical formulations. The compounds are present in the formulations at concentrations of about 0.0001 to 1.0 weight percent (wt. %), preferably 0.0001 to 0.1 wt. %, and most preferably about 0.0005 to 0.01 wt. %.

The compositions may contain other ingredients known to those skilled in the art of contact lens care solutions and/or ophthalmic pharmaceutical formulations.

The compounds of the present invention overcome some problems associated with prior antimicrobial compounds, such as benzalkonium chloride (BAC). Specifically, the use of BAC has the potential for inducing a toxic response, particularly after long term use.

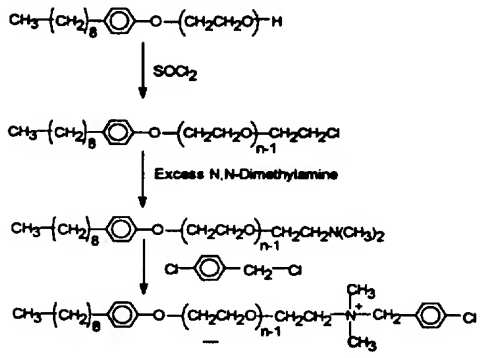
Without intending to be bound by any theory it is believed that the polyalkylene oxide moieties of the quaternary ammonium compounds of the present invention are responsible for the compounds producing a relatively low toxic response in ophthalmic applications. It is also believed that the polyalkylene moieties decrease the interaction of the quaternary ammonium group of the compounds with other compounds of the ophthalmic formulations or the environment to which the ophthalmic formulation is applied. It is postulated that the electron donor properties of the polyalkylene oxide moiety interact with the quaternary ammonium group (an electron acceptor group) thereby decreasing the interaction of the quaternary ammonium group with other compounds. Furthermore, the polyalkylene oxide containing polymers have been used to reduce the interaction of polymers with biomaterials. The following data shows that the above compounds are active even in the presence of the sodium salt of polystyrene sulfonate while marked reduction in antimicrobial activity was observed from BAC under the same experimental conditions.

Survival Count of P. aeruginosa
in the Presence of BAC and Compound B*

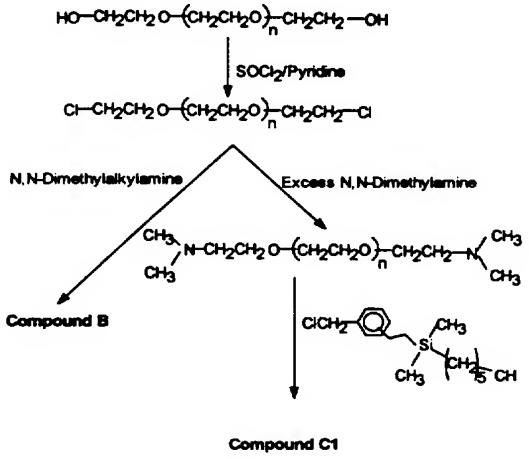
| Time (hr.) | BAC 0.05 % | Compound B (n=6, m=11, A=Cl) 0.05 % |
|---|---|---|
| 0 | $1.2 \times 10^6$ | $1.1 \times 10^6$ |
| 1 | $1.2 \times 10^6$ | $1.2 \times 10^6$ |
| 6 | $8.0 \times 10^5$ | $1.0 \times 10^5$ |
| 24 | $2.7 \times 10^5$ | < 10 |
| 48 | $1.7 \times 10^5$ | < 10 |
| 70 | $1.3 \times 10^6$ | < 10 |
| 14 Days | $1.5 \times 10^6$ | < 10 |

* The above formulations also contain the sodium salt of polystyrene sulfonate.

Two general schemes were employed to synthesize the compounds of the present invention. The monoquat compounds [A] were prepared starting from an aromatic substituted polyethylene oxide. An excellent starting compound was found to be p - nonylphenol polyethylene oxide. This compound was obtained as surfonic N-120 and N-60. The SURFONIC® N series of compounds, available from Texaco, are reaction products or adducts of nonylphenol and ethylene oxides. This was reacted with thionyl chloride and then converted to a tertiary amine and then the quaternary ammonium compound according to the following general scheme.




The diquat compounds such as [B] and [C] were prepared starting with hydroxy terminated polyalkylene oxides in the following general scheme of reactions.



## Example 1

Synthesis of Compound A (n=10)

Surfonic N-120 (6.55 g, 0.01 moles, from Texaco, Austin, TX) was reacted with 1.38 g (0.01 moles) of thionylchloride and 0.88 g (0.01 moles) of pyridine in 150 mL of toluene under reflux condition for 6 hrs. A precipitate was formed. The decanted organic layer was concentrated in vacuo and dissolved in chloroform (80 mL). This organic solvent was washed with satd. NaCl (10 mL X 3), dried over anhydrous $Na_2SO_4$, and evaporated to leave a liquid material (6 g). IR indicated no OH groups in the molecule.

The above chlorine compound (5 g, 0.0076 moles) was reacted with an excess amount of N,N-dimethylamine in 30 mL of dry THF (dried over LAH) under the pressure at 70°C for 24 hrs. and filtered. The filtrate was concentrated in vacuo and dissolved in chloroform (50 mL). This was washed with saturated NaCl solution and evaporated in vacuo to leave the corresponding tertiary amine (5 g, 100% yield). NMR spectrum shows singlet at 2.3 ppm for $N(CH_3)_2$.

The tertiary amine (2.27 g, 0.0034 mole) was then reacted with p-chlorobenzyl chloride (0.54 g, 0.0034 mole) in 20 mL of isopropanol under reflux conditions for 7 hrs. The concentrated reaction mixture was applied on a preparative $C_{18}$ reverse phase column with acetonitrile:$H_2O$ (70:30) was used as an eluent. The corresponding fraction was collected and concentrated in vacuo to leave 1.5 g (51.9% yield) of the product: Elemental Analysis: Calcd. for $C_{48}H_{83}Cl_{12}NO_{12}$•1 1/2 $H_2O$:C, 59.80; H, 8.99; N, 1.45; Cl, 7.35; O, 19.91. Found: C, 59.90; H, 8.91; N, 1.61 NMR ($CDCl_3$) δ 7.55 and 6.75 (2d, 4, $C_6H_4$), 7.3-7.0 (broad, 4, $C_6H_4$), 5.0 (s, 2, ∅-$CH_2$), 4.1-3.4 (48, $OCH_2CH_2$), 3.3 (s, 6, N-$CH_3$) and 1.7-0.4 (19,$(CH_2)_8CH_3$).

## Example 2

**Synthesis of Compound B (n=6, m=11, A=Cl)**

By following the same procedure as described for the synthesis of A(n=10) with polyethylene oxide (molecular weight 400) 20 g (0.05 moles) was reacted with 6.6 g (0.055 moles) of thionyl chloride and 4.9 g (0.055 moles) of pyridine in 200 mL of toluene 20 g. (100% yield) of the product is obtained. No appreciable amount of hydroxyl group was detected by IR spectrum.

The above dichloro compound (4.0 g, 0.01 moles) was reacted with an excess amount of N,N-dimethyldodecyl amine at 130°C for 24 hrs with stirring to afford 7.0 g (83.9% yield) of the quat compound: Elemental Analysis: Calcd. for $C_{42}H_{86}N_2O_9Cl_2$ (834.05)•$H_2O$:C, 59.21; H, 10.41; N, 3.29. Found: C, 59.21; H, 10.70; N, 3.11. NMR ($CDCl_3$) δ 4.0-3.4 (broad, 40, $OCH_2CH_2$ and N-$CH_2$), 3.35 (s, 6, N-$CH_3$), 1.7 (broad, 4, -N-$CH_2CH_2$), 1.4-1.1 (app 25, 36, $(CH_2)_n$), and 0.8 (t, 6, -$CH_2$-$CH_3$).

## Example 3

**Synthesis of Compound C3 (n=6)**

The polyethylene oxide (MW 400) dichloro compound (2.45 g, 0.0061 moles) was reacted with 3.78 g (0.0127 moles) of n-(N,N-dimethylethyl)-tetradecanoyl amide (synthesized from myristoyl chloride and N,N-dimethylethylenediamine) at 125°C for 6 hrs. Purification by ethyl ether afforded 1.8 g (30% yield) of the desired product: Elemental Analysis: Calcd. for $C_{54}H_{112}N_4O_{10}Cl_2$ (1048.36)•1 $H_2O$ C, 60.82; H, 10.79; N, 5.25. Found: C, 60.62; H, 10.83; N, 5.20. NMR ($CDCl_3$) δ 8.7 (broad s, 2, N-H), 3.8 (m, 44, $CH_2CH_2O$ and $N^+$-$CH_2$), 3.4 (d, 12, N-$CH_3$), 2.2 (t, 4, $CH_2$-C(=O)-), 1.6 (t, 4, C(=O)$CH_2CH_2$), 1.2 (s, 30, $(CH_2)_{10}$-$CH_3$) and 0.9 (t, 6, $CH_3$).

## Example 4

**Synthesis of Compound C2 (n=6)**

Following the same procedure as described for the synthesis of Compound C3 with 3.0 g (0.012 moles) of N-(N,N-dimethylethyl)-nonanoylamide (synthesized from nonanoyl chloride and N,N-dimethylethylene diamine) and 1.57 g (0.0038 moles) of polyethylene oxide (m.w. 400) - dichlo compounds, 2.2 g (59% yield) of the product was obtained. Elemental Analysis: Calcd. for $C_{44}H_{92}N_4O_9C1_2$: C, 59.29; H, 10.40; N, 6.29: Found: C, 59.37; H, 10.71; N, 6.42. NMR ($CDC1_3$) δ 8.7 (broad s, 2, NH), 3.8 (m, 40, $CH_2CH_2O$- and $N^+$-$CH_2$); 3.4 (s, 12, $N^+$-$CH_3$), 0.9 (t, 6, $CH_3$), 2.3 (t, 4, C-$CH_2$), 1.6 (m, 4, N-$CH_2CH_2$), 1.3 (broad s, 24, $CH_3$-($CH_2$)), 0.9 (s, 6, $CH_3$).

## Example 5

**Synthesis of Compound C1 (n=6)**

The polyethylene oxide (molecular weight 400) dichloro compound (5.1 g, 0.013 moles) was reacted with an excess amount of dimethylamine in 20 mL of tetrahydrofuran at 85°C for 16 hrs under pressure and concentrated in vacuo to remove the solvent. The remaining material was dissolved in ethylacetate and washed with saturated NaC1 Solution. This reaction yielded 2.9 g (57%) of the desired tetramethyl-diamine compound. The structure has confirmed by NMR and IR spectra.

The above compound (2.3 g, 0.0058 moles) was reacted with (m.p.)-dimethylhexylsilylethylbenzyl chloride (3.9 g, 0.0131 moles) in 40 mL of isopropanol under reflux condition for 6 hrs. This reaction afforded 2.9 g (50.9% yield) of the desired product. Elemental Analysis: Calcd. for $C_{56}H_{106}N_2O_8\ Si_2C1_2$ (1062.50)•1 $H_2O$:C, 62.24; H, 10.07; N, 2.59. Found: C, 62.49; H, 10.24; N, 2.67. NMR ($CDC1_3$) δ 7.4 (m, 8, -∅-), 5.0 (s, 4, -∅-$CH_2$-$N^+$), 3.6 (m, 36, $OCH_2CH_2$) 3.4 (s, 12, $N^+CH_3$).

The degree of polymerization, represented in the above compounds by n, is an expression of the number of structural units in a given polymer molecule. This number actually represents the average degree of polymerization as all the molecules will not have the same n. This invention is also directed to the use of polymers with an exact molecular weight, that is, no distribution of molecular weight. New procedures for making the exact molecular weight polymers are set forth below.

The following examples are directed to synthesis of exact molecular weight compounds. Compounds $B_4$ and $B_6$ are most preferred.

**Example 6**

**Synthesis of Exact Molecular Weight PEO Spacer Compounds**

| Compound | m | n | A |
|---|---|---|---|
| $B_1$ | 13 | 2 | Cl |
| $B_2$ | 13 | 2 | Br |
| $B_3$ | 13 | 4 | Cl |
| $B_4$ | 13 | 4 | Br |
| $B_5$ | 13 | 6 | Br |
| $B_6$ | 11 | 4 | Br |

a) Compound $B_1$

16.00 g (82.4 mM) of tetraethylene glycol was reacted with 16.30 g (206 mM) of pyridine and 24.50 g (206 mM) of thionyl chloride in dry chloroform (200 mL) at 65°C for 5 hrs. The reaction was neutralized by addition of aq $NaHCO_3$ and the organic phase washed with water (2 X 25 mL) then dried ($MgSO_4$). The filtrate was concentrated and the residue distilled under reduced pressure ($bp_{10}$ 84-85°C) to provide 15.63 g (82%) of tetraethylene glycol dichloride as a clear oil. 1.04 g (4.5 mM) of tetraethylene glycol dichloride was reacted with 2.44 g (10.12 mM) of N,N-dimethyltetradecylamine in 0.3 g

of DMSO and heated at 100°C for 18 hrs. Upon cooling the solidified reaction product was crystallized from ethyl acetate followed by recrystallization from ethyl acetate and ethanol to give 0.9 g (28%) of **$B_1$** as white crystals, mp 106-108°C. $^1$H NMR (200 MHz, $CDCl_3$): δ 4.1-3.6 (broad, 20 H, $OCH_2CH_2$, $NCH_2$), 3.45 (S, 12 H, N-$CH_3$), 1.72 (broad, 4 H, $NCH_2CH_2$), 1.4-1.2 (broad, 44 H, $(CH_2)_n$), 0.88 (t, 6 H, -$CH_2CH_3$). Anal. Calcd. for $C_{40}H_{86}Cl_2N_2O_3$•(1.25 $H_2O$): C, 65.23; H, 12.14; N, 3.92; Found: C, 65.29; H, 12.08; N, 3.84.

b) Compound **$B_3$**

15.00 g (53.1 mM) of hexaethylene glycol was reacted with 14.10 g (178 mM) of pyridine and 20.8 g (175 mM) of thionyl chloride in dry chloroform (200 mL) at 65°C for 5 hrs. The reaction was neutralized by addition of aq $NaHCO_3$ and the organic phase washed with water (2 X 25 mL) then dried ($MgSO_4$). The filtrate was concentrated and the residue distilled under reduced pressure ($bp_{10}$ 147-152°C) to provide 11.63 g (69%) of hexaethylene glycol dichloride as a clear oil. 4.8 g (15.0 mM) of hexaethylene glycol dichloride was reacted with 8.81 g (36.5 mM) of N,N-dimethyltetradecylamine in 2 g of DMSO and heated at 125°C for 15 hrs. The solidified reaction product was dissolved in ethyl acetate and precipitated with hexane (X 3) to remove DMSO then crystallized from ethyl acetate followed by recrystallization from ethyl acetate and ethanol to give 6.19 g (51%) of **$B_3$** as white crystals. $^1$H NMR (200 MHz, $D_2O$): δ 3.96-3.32 (broad, 28 H, $OCH_2CH_2$, $NCH_2$.), 3.13, 3.09 (2S, 12 H, N-$CH_3$), 1.75 (broad, 4 H, $NCH_2CH_2$.), 1.4-1.2 (broad, 44 H, $(CH_2)_n$), and 0.86 (t, 6 H, -$CH_2CH_3$).

c) Compound **$B_2$**

10.48 g (53.9 mM) of tetraethylene glycol was reacted with 10.28 g (130 mM) of pyridine and 27.0 g (130 mM) of thionyl bromide in dry chloroform (100 mL) at 70°C for 5 hrs. The reaction was neutralized by addition of aq $NaHCO_3$ and the organic phase washed with water (2 X 25 mL) then dried ($MgSO_4$). The filtrate was concentrated and a resulting sulfur precipitate removed by addition of chloroform and filtration through Celite. The filtrate was concentrated and the residue distilled under reduced pressure ($bp_{10}$ 100°C) to provide 7.71 g (45%) of tetraethylene glycol dibromide as an amber oil. 2.20 g (6.88 mM) of tetraethylene glycol dibromide was reacted with 3.65 g (15.1 mM) of N,N-

dimethyltetradecylamine in 0.5 g of DMSO at 90°C for 15 hrs. The solidified reaction product was crystallized twice from ethyl acetate to give 3.93 g (71%) of $\mathbf{B_2}$ as amber crystals. $^1$H NMR (200 MHz, $D_2O$): δ 4.0-3.4 (broad, 20 H, $OCH_2CH_2$, $NCH_2$), 3.19 (S, 12 H, N-$CH_3$), 1.8 (broad, 4 H, $NCH_2CH_2$-), 1.4-1.2 (broad, 44 H, $(CH_2)_n$), and 0.86 (t, 6 H, -$CH_2CH_3$). Anal. Calcd. for $C_{40}H_{86}Br_2N_2O_3$•(0.5 $H_2O$): C, 59.17; H, 10.80; N, 3.45; Found: C, 59.40; H, 10.54; N, 3.52.

d) Compound $\mathbf{B_4}$

9.44 g (33.4 mM) of hexaethylene glycol was reacted with 6.38 g (80.7 mM) of pyridine and 16.76 g (80.6 mM) of thionyl bromide in dry chloroform (100 mL) at 65°C for 3 hrs. The reaction was neutralized by addition of water and stirred for 30 minutes followed by washing of the organic phase with water until slightly acidic (2 X 25 mL, pH = 4-5). The organic phase was dried ($MgSO_4$), the filtrate concentrated and a resulting sulfur precipitate removed by addition of methanol and filtration through Celite (X 2). The filtrate was concentrated and the residue was dried in vacuo to provide 8.85 g (65%) of hexaethylene glycol dibromide as an amber oil. 2.26 g (5.53 mM) of hexaethylene glycol dibromide was reacted with 2.94 g (12.2 mM) of N,N-dimethyltetradecylamine in 0.6 g of DMSO at 90°C for 15 hrs. The solidified reaction product was crystallized from ethyl acetate followed by recrystallization from ethyl acetate and ethanol to give 3.17 g (64%) of $\mathbf{B_4}$ as white crystals, mp 95-97°C. $^1$H NMR (200 MHz, $D_2O$): δ 4.0-3.4 (broad, 28 H, $OCH_2CH_2$, $NCH_2$-), 3.15 (S, 12 H, N-$CH_3$), 1.78 (broad, 4 H, $NCH_2CH_2$-), 1.4-1.2 (broad, 44 H, $(CH_2)_n$), and 0.86 (t, 6 H, -$CH_2CH_3$). Anal. Calcd. for $C_{44}H_{94}Br_2N_2O_5$: C, 59.31; H, 10.63; N, 3.14; Found: C, 59.20; H, 10.59; N, 3.11.

e) Compound $\mathbf{B_5}$

The synthesis of octaethylene glycol was performed by following the procedure reported in *J. Org. Chem.*, 57, 6678, (1992) (Erik M. D. Keegstra, et al.): trityl chloride was reacted with excess diethylene glycol to make a monotritylated diethylene glycol intermediate (yield: 87%) followed by reaction of two equivalents of the monotritylated compound with one equivalent of tetraethylene glycol di-*p*-tosylate to form the ditritylated octaethylene glycol intermediate (yield: 95%) which was then converted to octaethylene glycol by hydrogenolysis with hydrogen and palladium on charcoal catalyst (purity:

97.2%, by GC yield: 90%). Overall yield was 74%. 4.47 g (12.1 mM) of octaethylene glycol was reacted with 2.30 g (29.1 mM) of pyridine and 6.07 g (29.2 mM) of thionyl bromide in dry chloroform (100 mL) at 50°C for 5 hrs. The reaction was neutralized by addition of water (25 mL) and stirred for 30 minutes followed by washing of the organic phase with water until slightly acidic (3 X 20 mL, pH = 4-5). The organic phase was dried ($MgSO_4$), the filtrate concentrated and the resulting sulfur precipitate removed by addition of methanol and filtration through Celite (X 2). The filtrate was concentrated and the residue dried in vacuo to provide 4.41 g (74%) of octaethylene glycol dibromide as an amber oil. 2.91 g (5.86 mM) of octaethylene glycol dibromide was reacted with 3.12 g (12.9 mM) of N,N-dimethyltetra-decylamine in 0.7 g of DMSO at 80°C for 15 hrs. The solidified reaction product was crystallized from ethyl acetate followed by recrystallization from ethyl acetate and ethanol to give 4.0 g (70%) of $\mathbf{B_5}$ as white crystals. $^1$H NMR (200 MHz, $D_2O$): $\delta$ 4.0-3.35 (broad, 36 H, $OCH_2CH_2$ $NCH_2$.), 3.15 (S, 12 H, N-$CH_3$), 1.76 (broad, 4 H, $NCH_2CH_2$.), 1.4-1.2 (broad, 44 H, $(CH_2)_n$), 0.86 (t, 6 H, -$CH_2CH_3$). Anal. Calcd. for $C_{48}H_{102}Br_2N_2O_7$: C, 58.88; H, 10.50; N, 2.86; Found: C, 58.56; H, 10.28; N, 2.89.

f) Compound $\mathbf{B_6}$

1.65 G (4.0 mM) of hexaethylene glycol dibromide was reacted with 1.90 g (8.9 mM) of N,N-dimethyldodecylamine in 0.44 g of DMSO and heated at 80°C for 15 hrs. The solidified reaction product was crystallized from ethyl acetate followed by recrystallization from ethyl acetate and ethanol to give 1.85 g (55%) of $\mathbf{B_6}$ as white crystals, mp 83-85°C. $^1$H NMR (200 MHz, $D_2O$): $\delta$ 4.0-3.35 (broad, 28 H, $OCH_2CH_2$, $NCH_2$.), 3.15 (S, 12 H, N-$CH_3$), 1.8 (broad, 4 H, $NCH_2CH_2$.), 1.4-1.2 (broad, 36 H, $(CH_2)_n$), 0.86 (t, 6 H, -$CH_2CH_3$). Anal. Calcd for $C_{40}H_{86}Br_2N_2O_5$: C, 57.54; H, 10.38; N, 3.36; Found: C, 57.68; H, 10.42; N, 3.30.

**Log Reduction of 0.001% Compounds***

| | *A. fumigatus* | | *S. marcescens* | |
|---|---|---|---|---|
| **Compound** | **6 hrs** | **24 hrs** | **6 hrs** | **24 hrs** |
| $B_1$ | 1.6 | 1.7 | 3.0 | 4.8 |
| $B_2$ | 1.7 | 2.6 | 2.9 | 4.1 |
| $B_3$ | 2.1 | 2.4 | 4.0 | 6.8 |
| $B_4$ | 1.4 | 2.7 | 3.2 | 3.9 |
| $B_5$ | 2.4 | 2.7 | 3.5 | 5.6 |
| $B_6$ | 2.2 | 3.2 | 2.2 | 3.7 |

* in 0.58% boric acid, 0.05% disodium EDTA, 0.18% sodium borale, 0.49% sodium chloride at pH 7.0

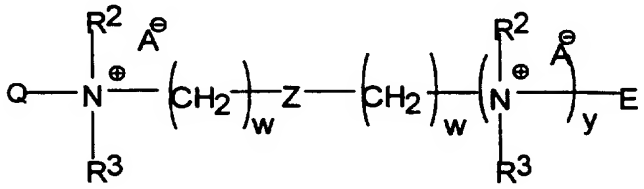
**Example 7**

**Preserved Saline or Contact Lens Disinfecting Formulations**

| **Ingredient** | **Concentration** |
|---|---|
| Boric Acid | 0.58% |
| Sodium Borate | 0.18% |
| Sodium Chloride | 0.49% |
| Disodium EDTA | 0.10% |
| Compound $B_5$ | 0.001% |
| Tetronic 1304 | 0.1% |
| NaOH/HCl | pH 7.4 |
| Purified Water | q.s. |

We claim:

1. A contact lens formulation comprising a compound having the structure:



wherein:

w = 0-10;

y = 0 or 1;

$R^2$ and $R^3$ are the same, or different, and are selected from the group: $C_1$-$C_{20}$ alkyl, benzyl and substituted benzyls, aromatics and substituted aromatics and cycloalkyl and substituted cycloalkyls; Q and E are the same, or different, and are selected from the group: H, $C_1$-$C_{20}$ alkyl, $C_2$-$C_6$ alkene, benzyl and substituted benzyls, aromatics and substituted aromatics, cycloalkyl and substituted cycloalkyls; heteroatom containing long alkyl chain, silane and siloxane; but, either Q and/or E must contain an alkyl structure of at least a $C_5$ alkyl, but not more than a $C_{20}$ alkyl moiety; Z has the following structure:

$$[(CH_2\text{-}CH(R)\text{-}O)_n\text{-}(CH_2\text{-}CH(R')\text{-}O)_m]_x$$

wherein:

R and R' are different and can be H, methyl or ethyl;

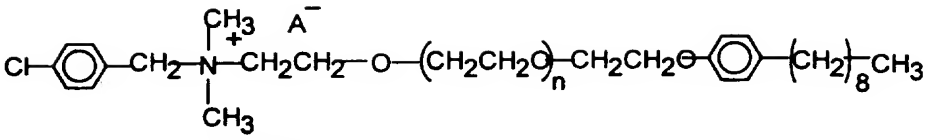
n = 1-4

m = 0-4

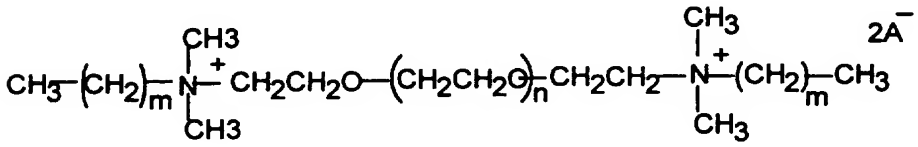
x = 1-50; and

$A^-$ is a pharmaceutically acceptable anion.

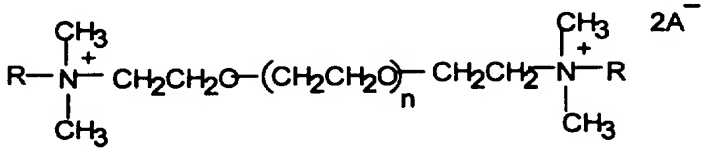
2. The formulation of Claim 1 wherein the compound is selected from the group consisting of



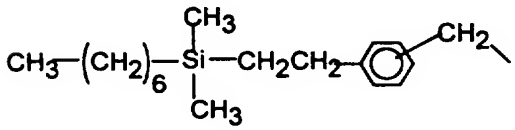
wherein n = 4-13



wherein m = 7-17, n = 0-14



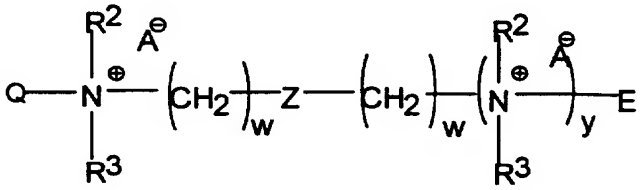
wherein R and n are as defined below:

| R | n |
|---|---|
|  | 6-8 |
|  | 6-8 |
|  | 6-8 |

3. The formulation of Claim 1 wherein the compound is present at a concentration of 0.0001% to 1.0%.

4. The formulation of Claim 3 wherein the compound is present at a concentration of 0.0005% to 0.01%.

5. An ophthalmic formulation comprising a compound having the structure



wherein:

w = 0-10;

y = 0 or 1;

$R^2$ and $R^3$ are the same, or different, and are selected from the group: $C_1$-$C_{20}$ alkyl, benzyl and substituted benzyls, aromatics and substituted aromatics and cycloalkyl and substituted cycloalkyls; Q and E are the same, or different, and are selected from the group: H, $C_1$-$C_{20}$ alkyl, $C_2$-$C_6$ alkene, benzyl and substituted benzyls, aromatics and substituted aromatics, cycloalkyl and substituted cycloalkyls; heteroatom containing long alkyl chain, silane and siloxane; but, either Q and/or E must contain an alkyl structure of at least a $C_5$ alkyl, but not more than a $C_{20}$ alkyl moiety; Z has the following structure:

$$[(CH_2\text{-}CH(R)\text{-}O)_n\text{-}(CH_2\text{-}CH(R')\text{-}O)_m]_x$$

wherein:

R and R' are different and can be H, methyl or ethyl;

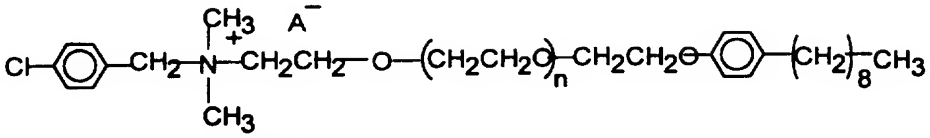
n = 1-4

m = 0-4

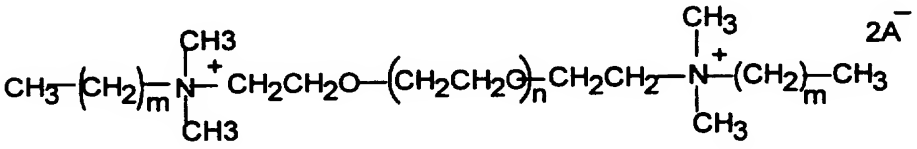
x = 1-50; and

$A^-$ is a pharmaceutically acceptable anion.

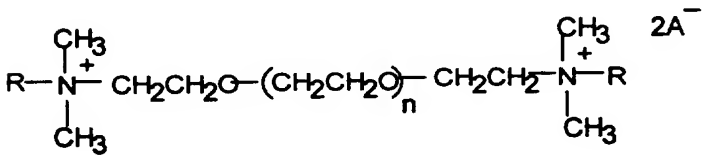
6. The formulation of Claim 5 wherein the compound is selected from the group consisting of



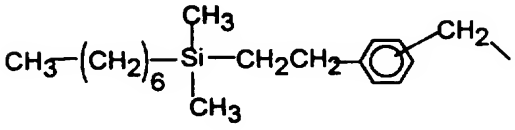
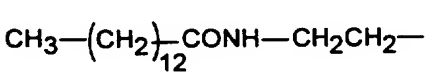
wherein n = 4-13



wherein m = 7-17, n = 0-14



wherein R and n are as defined below:

| R | n |
|---|---|
|  | 6-8 |
|  | 6-8 |
|  | 6-8 |

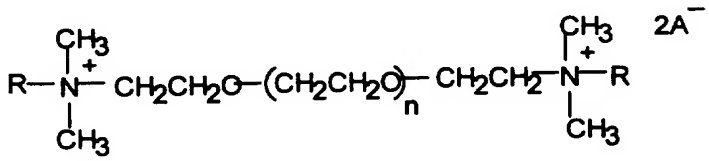
7. The formulation of Claim 5 wherein the compound is present at a concentration of 0.0001% to 1.0%.

8. The formulation of Claim 7 wherein the compound is present at a concentration of 0.0005% to 0.01%.

9. A method for disinfecting a contact lens; which comprises, applying the composition of Claim 1 to the lens.

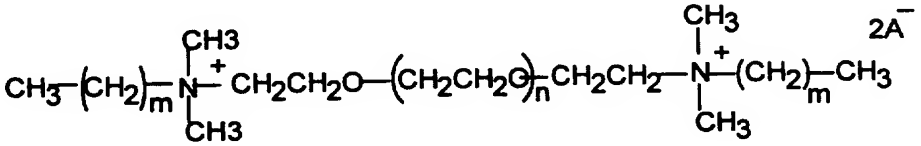
10. A method for preserving an ophthalmic formulation by adding a compound of Claim 5 to the formulation.

11. A compound of the formula



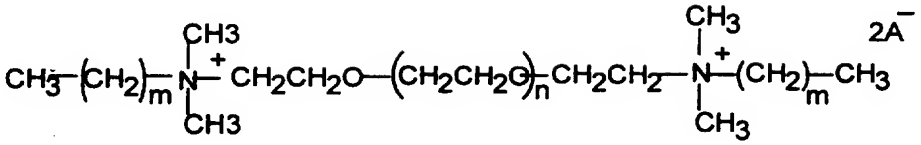
wherein R is $CH_3$-$(CH_2)_6$-$Si(CH_3)_2$-$CH_2$-$CH_2$-Ar-$CH_2$-, n is an integer from 6 to 8 and A- is a pharmaceutically acceptable anion.

12. A compound of the formula



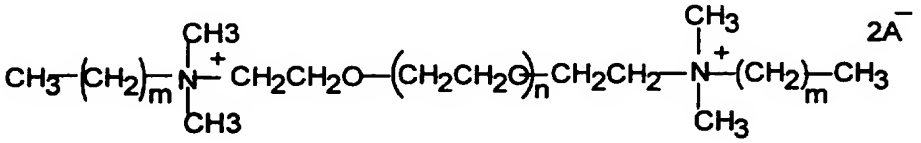
wherein m is 13, n is 2 and A is Cl having a molecular weight of 714.05.

13. A compound of the formula



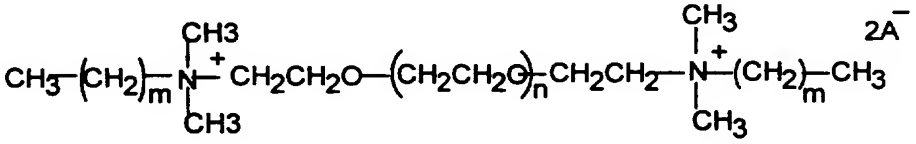
wherein m is 13, n is 2 and A is Br having a molecular weight of 802.95.

14. A compound of the formula



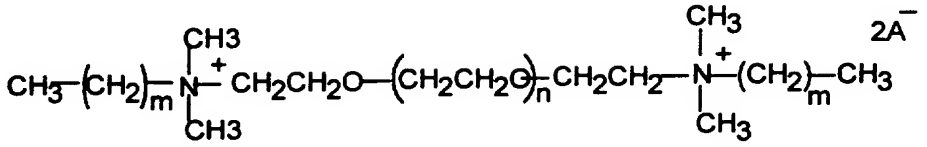
wherein m is 13, n is 4 and A is Cl having a molecular weight of 802.16.

15. A compound of the formula



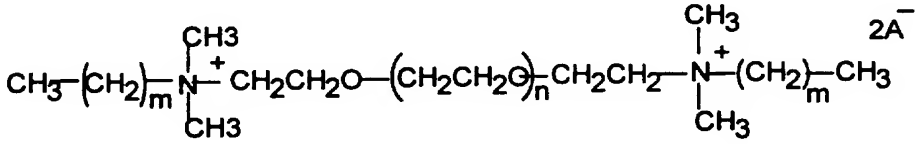
wherein m is 13, n is 4 and A is Br having a molecular weight of 891.06.

16. A compound of the formula



wherein m is 13, n is 6 and A is Br having a molecular weight of 979.17.

17. A compound of the formula



wherein m is 11, n is 4 and A is Br having a molecular weight of 834.95.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09724

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :514/616, 642, 643, 912, 915; 556/423; 564/159, 282, 286, 287, 294
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/616, 642, 643, 912, 915; 556/423; 564/159, 282, 286, 287, 294

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO, A, 91/09522 (ALLERGAN, INC.) 11 July 1991, see entire document. | 1-10, 12-17 |
| Y | US, A, 5,242,684 (MERIANOS) 07 September 1993, see entire document. | 1-10, 12-17 |
| Y | US, A, 4,567,302 (SIVARAMAKRISHNAN) 28 January 1986, see entire document. | 1, 3-5, 7-10 |
| Y | US, A, 4,110,263 (LINDEMANN ET AL.) 29 August 1978, see entire document. | 1-10, 12-17 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
15 NOVEMBER 1995

Date of mailing of the international search report
28 NOV 1995

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Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09724

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/135, 31/14, 31/16, 31/695; C07C 217/42, 217/48, 217/58, 233/36; C07F 7/10